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☐	L4	L3 and (plasmid or vector)	822
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END OF SEARCH HISTORY

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DOCUMENT-IDENTIFIER: US 6872547 B1
TITLE: Functional balanced-lethal host-vector systems

CLAIMS:

1. An attenuated derivative of a pathogenic microorganism which comprises: (a) a non-functional native chromosomal essential gene; (b) a recombinant complementing gene on an extrachromosomal vector, wherein the complementing gene can recombine to replace the non-functional native chromosomal essential gene; and (c) a desired gene on the extrachromosomal vector, wherein the desired gene is a recombinant gene encoding a desired gene product; wherein said complementing gene of (b) is a functional replacement for said essential gene of (a), wherein the desired gene is stably maintained in a progeny population of the microorganism.

2. The microorganism of claim 1, wherein the microorganism is a member of the Enterobacteriaceae and the extrachromosomal vector is a plasmid.

3. The microorganism of claim 2, further comprising an inactivating mutation in a gene selected from the group consisting of a pab gene, a pur gene, an aro gene, nadA, pncB, galE, pmi, fur, rpsL, ompR, htrA, hemA, cdt, cya, crp, dam, phoP, phoQ, rfc, poxA, galU, mvlA, sodC, recA, ssrA, sirA, inv, hilA, rpoE, flgM, tonB, and slyA.

4. The microorganism of claim 3, wherein the desired gene product is an antigen.

6. The microorganism of claim 2, wherein the essential gene is selected from the group consisting of dapA, dapB, depD, depE, dapF, and asd.

7. The microorganism of claim 6, wherein the non-functional native chromosomal essential gene is an asd gene wherein said asd gene comprises an insertion or a deletion.

8. The microorganism of claim 2, wherein the recombinant complementing gene lacks an RNA polymerase -35 recognition sequence and a promoter -10 sequence.

9. The microorganism of claim 8, wherein the recombinant complementing gene is an asd gene.

10. The microorganism of claim 2, wherein the desired gene is operably linked to a eukaryotic promoter.

12. A recombinant vector comprising a recombinant complementing gene, wherein the recombinant complementing gene lacks an RNA polymerase -35 recognition sequence and a promoter -10 sequence, wherein the recombinant complementing gene is a functional replacement for a non-functional native chromosomal essential gene when the vector is present in a microorganism having a non-functional native chromosomal essential gene.

13. The recombinant vector of claim 12, wherein the vector is a plasmid capable of expressing the recombinant complementing gene in a microorganism that is a member of the Enterobacteriaceae.

14. The recombinant vector of claim 12, wherein the recombinant complementing gene encodes an enzyme that catelyzes a step in the biosynthesis of DAP (mesodiaminopimellc acid).

15. The recombinant vector of claim 14, wherein the recombinant complementing gene is an asd gene.

16. The recombinant vector of claim 12, further comprising a gene encoding a desired gene product.

17. The recombinant vector of claim 16, wherein the desired gene product is an antigen.

18. The recombinant vector of claim 17, wherein the antigen is selected from the group consisting of a bacterial antigen, a viral antigen, a fungal antigen, a parasitic antigen, a gamete-specific antigen, an allergen, and a tumor antigen.

19. The recombinant vector of claim 16, wherein the desired gene product is therapeutic to a vertebrate.

20. The recombinant vector of claim 19, wherein the desired gene product is selected from the group consisting of a lymphokine, a cytokine, and a sperm-specific or egg-specific autoantigen.

21. The recombinant vector of claim 16, wherein the desired gene product is operably linked to a eukaryotic promoter.

22. The recombinant vector of claim 21, wherein the eukaryotic promoter is a CMV promoter.

23. An attenuated derivative of a pathogenic microorganism which comprises: (a) a mutation of a polynucleotide sequence that renders a native chromosomal essential gene non-functional; (b) a recombinant complementing gene on an extrachromosomal vector, wherein the complementing gene is functional replacement for said essential gene of (a) and wherein said complementing gene can recombine to replace the essential gene of (a); and (c) a desired gene on the extrachromosomal vector, wherein the desired gene is a recombinant gene encoding a desired gene product; wherein the desired gene is stably maintained in a progeny population of the microorganism.

24. An attenuated derivative of a pathogenic microorganism which comprises: (a) a non-functional native chromosomal essential gene; (b) a recombinant complementing gene on an extrachromosomal vector, wherein the complementing gene can recombine to replace the non-functional chromosomal essential gene; (c) a desired gene on the extrachromosomal vector, wherein the desired gene is a recombinant gene encoding a desired gene product; and (d) an inactivating mutation in a native gene selected from the group consisting of a pab gene, a pur gene, and ar gene, nadA, pncB, gale, pmi, fur, rpsL, ompR, htrA, hemA, cdt, cya, crp, dam, phoP, phoQ, rfc, poxA, falU, mviA, sodC, recA, ssrA, sirA, inv, hilA, rpoE, flgM, tonB, and slyA; wherein said complementing gene of (b) is a functional replacement for herein the desired gene is stably maintained in a progeny population of the microorganism.

DOCUMENT-IDENTIFIER: US 6399856 B1
TITLE: Reversible nuclear genetic system for male sterility in transgenic plants

CLAIMS:

1. A method for producing reversible male sterility in a plant, comprising the steps of:

(a) providing a first plant which is male sterile, said plant having a first genetic construct, said first genetic construct comprising (i) an operator that is capable of controlling expression of a dominant negative gene, (ii) a dominant negative gene that, when expressed in a plant, disrupts pollen formation or function, (iii) a first gene encoding a first DNA binding protein which can bind to the operator and activate transcription of said dominant negative gene, and (iv) a first promoter that drives transcription in cells critical to pollen formation or function, said first promoter regulating the transcription of said first gene encoding said first DNA-binding protein;

(b) providing a second plant which is male fertile, said second plant having a second genetic construct comprising a suitable second promoter controlling a second gene encoding a second DNA-binding protein, said second DNA-binding protein interacting with the operator of the first genetic construct, such that the transcription of the dominant negative gene is repressed; and

(c) crossing said first plant with said second plant to form a hybrid plant which is male fertile.

2. The method of claim 1, wherein said dominant negative gene is a cytotoxic gene.

3. The method of claim 1, wherein said dominant negative gene is a methylase gene.

4. The method of claim 3, wherein said methylase gene is a DAM methylase gene.

5. The method of claim 1, wherein said dominant negative gene is a growth-inhibiting gene.

6. The method of claim 1, wherein said dominant negative gene is a diphtheria toxin A-chain gene.

7. The method of claim 1, wherein said dominant negative gene is a cell division cycle mutant gene.

8. The method of claim 7, wherein said cell division cycle mutant gene is a CDC gene.

9. The method of claim 7, wherein said cell division cycle mutant gene is a WT gene.

10. The method of claim 7, wherein said cell division cycle mutant gene is a P68 gene.

15. The method of claim 1, wherein the operator is the lexA operator, the dominant negative gene is a DAM methylase gene, and the first promoter that drives transcription in cells critical to pollen formation or function is a 5126 promoter.

17. The method of claim 1, wherein said first genetic construct further comprises a selectable marker gene.

DOCUMENT-IDENTIFIER: US 6383496 B1
TITLE: Recombinant vaccines comprising immunogenic attenuated bacteria having RPOS positive phenotype

CLAIMS:

1. A method for producing, from a parent bacteria strain, a carrier bacteria for the delivery of a desired gene product to a human comprising generating a strain of bacteria comprsising (a) a recombinant rpoS.sup.+ gene; (b) one or more inactivating mutations which render said bacteria attenuated; and (c) a second recombinant gene encoding the desired gene product, wherein said carrier bacteria expresses a higher level of RpoS gene product than said parent bacteria strain and wherein said higher level of RpoS gene product confers upon the carrier bacteria high immunogenicity relative to said parent bacteria strain.

2. The method of claim 1, said bacteria lacks a functional chromosomal rpoS.sup.+ gene.

5. The method according to claim 4 wherein the one or more inactivating mutations are in a gene selected from the group consisting of a pab gene, a pur gene, an aro gene, asd, a dap gene, nadA, pncB, galE, pmi, fur, rpsL, ompR, htrA, hemA, cdt, cya, crp, dam, phoP, phoQ, rfc, poxA, galU, metL, metH, mviA, sodC, recA, ssrA, ssrB, sirA, sirB, sirC, inv, hilA, hilC, hilD, rpoE, flgM, tonB, and slyA.

6. The method according to claim 5 wherein the second recombinant gene encodes a gene product from a pathogen to said human.

8. A carrier bacteria for the delivery of a desired gene product to a human produced according to the method of claim 1.

9. The carrier bacteria of claim 8, wherein said bacteria lacks a functional chromosomal rpoS+ gene.

12. The carrier bacteria according to claim 11 wherein the one or more inactivating mutations are in a gene selected from the group consisting of a pab gene, a pur gene, an aro gene, asd, a dap gene, nadA, pncB, galE, pmi, fur, rpsL, ompR, htrA, hemA, cdt, cya, crp, dam, phoP, phoQ, rfc, poxA, galU, metL, metH, mviA, sodC, recA, ssrA, ssrB, sirA, sirB, sirC, inv, hilA, hilC, hilD, rpoE, flgM, tonB, and slyA.

13. The carrier bacteria according to claim 12 wherein the second recombinant gene encodes a gene product from a pathogen to said human.

16. The composition of claim 15, wherein said bacteria lacks a functional chromosomal rpoS+ gene.

19. The composition according to claim 18 wherein the one or more inactivating mutations are in a gene selected from the group consisting of a pab gene, a pur gene, an aro gene, asd, a dap gene, nadA, pncB, galE, pmi, fur, rpsL, ompR, htrA, hemA, cdt, cya, crp, dam, phoP, phoQ, rfc, poxA, galU, metL, metH, mviA, sodC, recA, ssrA, ssrB, sirA, sirB, sirC, inv, hilA, hilC, hilD, rpoE, flgM, tonB,and slyA.

20. The composition according to claim 19 wherein the second recombinant gene encodes a gene product from a pathogen to said human.

23. A genetically engineered bacterial cell, wherein said genetically engineered bacterial cell (a) is produced from a parent bacterial cell, (b) is a live attenuated strain of bacteria, (c) has a recombinant rpoS.sup.+ gene, (d) has one or more inactivating mutations which render said bacteria attenuated and

(e) has a second recombinant gene encoding a desired gene product, and wherein the genetically engineered bacterial cell expresses a higher level of RpoS gene product than said parent bacteria cell and wherein said higher level of RpoS gene product confers upon the genetically engineered bacterial cell high immunogenicity relative to said parent bacteria strain.

24. The genetically engineered bacterial cell of claim 23, wherein said bacterial cell lacks a functional chromosomal rpoS+ gene.

27. The genetically engineered bacterial cell according to claim 26 wherein the one or more inactivating mutations are in a gene selected from the group consisting of a pab gene, a pur gene, an aro gene, asd, a dap gene, nadA, pncB, galE, pmi, fur, rpsL, ompR, htrA, hemA, cdt, cya, crp, dam, phoP, phoQ, rfc, poxA, galU, metL, metH, mviA, sodC, recA, ssrA, ssrB, sirA, sirB, sirC, inv, hilA, hilC, hilD, rpoE, flgM, tonB, and slyA.

28. The genetically engineered bacterial cell according to claim 27 wherein the second recombinant gene encodes a gene product from a pathogen to said human.

31. The method of claim 30, wherein said bacterial cell lacks a functional chromosomal rpoS+ gene.

D1 AL08

10784160 PMID: 7986589

High-titer immune responses elicited by recombinant vaccinia **virus priming and particle boosting are** ineffective **in preventing virulent SIV infection.**

Daniel M D; Mazzara G P; Simon M A; Sehgal P K; Kodama T; Panicali D L; Desrosiers R C

New England Regional Primate Research Center, Harvard Medical School, Southborough, Massachusetts 01772-9102.

AIDS research and human retroviruses (UNITED STATES) Jul 1994, 10 (7) p839-51, ISSN 0889-2229 Journal Code: 8709376

Contract/Grant No.: AI26507; AI; NIAID; RR00168; RR; NCRR

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Languages: ENGLISH

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Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS; AIDS/HIV

Eighteen rhesus monkeys were vaccinated with recombinant vaccinia viruses expressing SIVmac antigens in 3 separate rounds of experiments. Twelve of the monkeys were primed with a trivalent vaccinia virus recombinant expressing Gag, Pol, and Env polypeptides that can assemble into SIV pseudovirion particles and boosted with SIV particles in adjuvant. Four of the monkeys were primed with different vaccinia virus recombinants expressing env or gag+env followed by SIV particle boosts; two received vaccinia virus recombinants alone (env or env+gag). Despite the induction of vigorous immune responses, 17 of 18 rhesus monkeys became infected on challenge with a low dose of virulent SIVmac. The single protected animal was one of three challenged with homologous cloned SIV exactly matched to the clone used for construction of trivalent vaccinia virus recombinant and particles. Vaccination may have diminished SIV burdens and rates of CD4+ cell declines in some of the animals, but vaccinated/challenge/infected animals eventually developed fatal disease similar to control animals. These results highlight the extreme difficulty in achieving vaccine protection against virulent SIVmac infection even under idealized laboratory conditions.

Tags: Research Support, U.S. Gov't, P.H.S.

Descriptors: *SAIDS Vaccines--administration and dosage--AD; *SIV --pathogenicity--PY; *Simian Acquired Immunodeficiency Syndrome--prevention and control--PC; Animals; Antibody Formation; Blotting, Western; CD4-Positive T-Lymphocytes--pathology--PA; Immunization, Secondary; Macaca mulatta; SIV--immunology--IM; Simian Acquired Immunodeficiency Syndrome --immunology--IM; Trachea--pathology--PA; Trachea--ultrastructure--UL; Vaccination; Virulence

CAS Registry No.: 0 (SAIDS Vaccines)

Record Date Created: 19950109

Record Date Completed: 19950109

13169075 PMID: 11188544

[Pneumococcal vaccine **for the elderly--** ineffective **but cost-efficient?]**

Pneumokockvaccination till aldre--overksam men kostnadseffektiv metod?

Hakansson J

Lakartidningen (Sweden) Dec 13 2000, 97 (50) p5958, ISSN 0023-7205 Journal Code: 0027707

Publishing Model Print; Comment on Lakartidningen. 2000 Nov 8;97(45) 5120-5; Comment on PMID 11116891

Document type: Comment; Letter

Languages: SWEDISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

Descriptors: *Pneumococcal Infections--prevention and control--PC; *Pneumococcal Vaccines--administration and dosage--AD; *Pneumococcal Vaccines--economics--EC; Aged; Cost-Benefit Analysis; Humans; Pneumonia, Pneumococcal--prevention and control--PC; Sweden

CAS Registry No.: 0 (Pneumococcal Vaccines)

Record Date Created: 20010116

Record Date Completed: 20010222

15120378 PMID: 14682168

[Cases of ineffective **anti-hepatitis B** vaccination **--own observations]**

Przypadki nieskutecznego szczepienia przeciw wirusowemu zapaleniu watroby typu B--obserwacje wlasne.

Kepa Lucjan; Oczko-Grzesik Barbara; Sobala-Szczygiel Barbara; Stolarz Wojciech; Wilczek Krzysztof; Mossor Krystyna; Warakomska Iwona; Dziambor Andrzej P

Oddzial Chorob Zakaznych Slaskiej Akademii Medycznej w Bytomiu.

Przeglad epidemiologiczny (Poland) 2003, 57 (3) p491-7, ISSN 0033-2100 Journal Code: 0413725

Publishing Model Print

Document type: Journal Article; Review; Review, Multicase ; English Abstract

Languages: POLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

Between 1999-2001 there were 6 patients with acute hepatitis B, previously vaccinated according to the recommended schedule of anti-hepatitis B immunization for adults, hospitalized in the Department of Infectious Diseases (Bytom, Silesian University Medical School). The study presents epidemiological and clinical analysis of these cases. Special attention is paid to possibility of immune response failure in spite of anti-hepatitis B vaccination. It is emphasized, that efficiency of active hepatitis B prophylaxis should be verified by estimation of serum anti-HBs antibodies, especially in patients with planned surgery. (22 Refs.)

Tags: Female; Male

Descriptors: *Hepatitis B Antibodies--blood--BL; *Hepatitis B Vaccines; *Hepatitis B virus--immunology--IM; *Hepatitis B, Chronic--prevention and control--PC; Adult; Hepatitis B Surface Antigens--immunology--IM; Hepatitis B Vaccines--adverse effects--AE; Hepatitis B, Chronic--immunology--IM; Humans; Middle Aged; Poland; Risk Factors; Time Factors

CAS Registry No.: 0 (Hepatitis B Antibodies); 0 (Hepatitis B Surface Antigens); 0 (Hepatitis B Vaccines)

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Ineffectiveness **of hepatitis B** vaccination **in cirrhotic patients waiting for liver transplantation.**

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Cirrhotic patients who undergo liver transplantation are at risk of acquiring de novo hepatitis B virus (HBV) infection at the time of transplantation. It is common practice to immunize these patients against HBV, but the efficacy of vaccination is uncertain. The response to vaccination with a recombinant HBV vaccine was examined in 49 patients with cirrhosis before liver transplantation. Patients received three doses (20 mg) of Engerix-B (SmithKline Beecham) at zero, one and two months before transplantation, and their response was measured on the day of liver transplantation (9.3+/-1.2 months after the initial dose of vaccine). Results were compared with those reported in healthy adults vaccinated according to the same schedule. Fourteen of 49 cirrhotic patients (28%) developed antibodies to hepatitis B surface antigen (anti-HBs) levels of more than 10 U/L after vaccination compared with 97% of healthy controls. Four patients (8%) had anti-HBs levels of more than 100 U/L compared with 83% in healthy individuals. Mean anti-HBs titre in the 14 responders was 62 U/L compared with 348 U/L in controls. No factor was identified that predicted response to vaccination. One of 49 patients acquired de novo HBV infection at the time of liver transplantation. Current HBV vaccination of cirrhotic patients waiting for liver transplantation is ineffective, and new strategies need to be developed to increase the response rate.

Tags: Female; Male; Research Support, Non-U.S. Gov't

Descriptors: *Hepatitis B--prevention and control--PC; *Hepatitis B Vaccines; *Liver Cirrhosis--surgery--SU; *Liver Transplantation--adverse effects--AE; Hepatitis B--etiology--ET; Humans; Liver Transplantation --methods--MT; Middle Aged; Retrospective Studies; Risk Factors; Treatment Failure

CAS Registry No.: 0 (Hepatitis B Vaccines)

Record Date Created: 20001019

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Internist (Berl). 2003 Jun;44(6):711-8. Related Articles, Links

[Status and current strategies of HIV vaccine development]

[Article in German]

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Despite intensive research efforts a vaccine against HIV has not yet been developed twenty years even after the onset of the HIV-epidemic. The problems in the development of an HIV-vaccine as well as former and current strategies to overcome these problems are presented here. The current status of human studies of different candidate vaccines is outlined.

Publication Types:
- Review
- Review, Tutorial

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HIV Vaccine Rationale, Design and Testing.

Slobod KS, Coleclough C, Bonsignori M, Brown SA, Zhan X, Surman S, Zirkel A, Jones BG, Sealy RE, Stambas J, Brown B, Lockey TD, Freiden PJ, Doherty PC, Blanchard JL, Martin LN, Hurwitz JL.

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A central obstacle to the design of a global HIV vaccine is viral diversity. Antigenic differences in envelope proteins result in distinct HIV serotypes, operationally defined such that antibodies raised against envelope molecules from one serotype will not bind envelope molecules from a different serotype. The existence of serotypes has presented a similar challenge to vaccine development against other pathogens. In such cases, antigenic diversity has been addressed by vaccine design. For example, the poliovirus vaccine includes three serotypes of poliovirus, and Pneumovax(R) presents a cocktail of 23 pneumococcal variants to the immune system. It is likely that a successful vaccine for HIV must also comprise a cocktail of antigens. Here, data relevant to the development of cocktail vaccines, designed to harness diverse, envelope-specific B-cell and T-cell responses, are reviewed.

[00232] In another embodiment, the invention provides methods for preparing an attenuated bacteria capable of eliciting an immunological response by a host susceptible to disease caused by the corresponding or similar pathogenic bacteria comprising (a) constructing a first non-reverting mutation in said pathogenic bacteria wherein said first non-reverting mutation alters the expression of or the activity of one or more DNA adenine methylases, and (b) constructing a second non-reverting mutation in said pathogenic bacteria wherein said second non-reverting mutation is independent of said first non-reverting mutation and is attenuating. In some embodiments, the first non-reverting mutation is constructed in a gene whose product activates one or more of said DNA adenine methylases. In some embodiments, the gene product activates DNA adenine methylase. In some embodiments, the first non-reverting mutation is constructed in a gene whose product represses the expression of said DNA adenine methylases. In some embodiments, said gene product represses DNA adenine methylase. In other embodiments, the first non-reverting mutation is constructed in a gene whose product inactivates or decreases the activity of one or more of said DNA adenine methylases by binding directly to one or more of said DNA adenine methylases. In some embodiments, one of said DNA adenine methylases is DNA adenine methylase. In some embodiments, the pathogenic bacteria is a strain of *Salmonella*, preferably *Salmonella* is *S. typhimurium, S. enteritidis, S. typhi, S. bortus-ovi, S. abortus-equi, S. dublin, S. gallinarum, S. pullorum.* In other embodiments, the pathogenic bacteria are any one of the following: *Yersinia, Vibrio, Shigella, Haemophilus, Bordetella, Neisseria, Pasteurella, pathogenic Escherchia, Treponema.* The host may be a vertebrate, such as a mammal, preferably human or a domestic animal. In some embodiments, the vertebrate is a chicken.

[00233] In some embodiments, the preparation methods comprise addition of an antigen. For example, the antigen can be added simply to the bacteria in the vaccine, or, alternatively, expression cassette comprising one or more structural genes coding for a desired antigen may be inserted into the attenuated bacteria.

[00234] Antigens include, but are not limited to, Fragment C of tetanus toxin, the B subunit of cholera toxin, the hepatitis B surface antigen, *Vibrio cholerae* LPS, HIV antigens and/or *Shigella soneii* LPS.

immune response. However, Dam⁻ bacteria may ectopically express multiple antigens that are processed and presented to the immune system, and thus, animals immunized with Dam⁻ vaccines may elicit stronger immune responses than animals that survive a natural infection.

[00271] The immunity elicited by the Dam⁻ vaccine was compared to the immunity elicited after a natural infection with the wild-type strain. BALB/c mice were orally immunized at the LD_{50} of the virulent strain *S. typhimurium* (10^{+5} organisms) (i.e., one half the mice survived the wild-type immunization) or 10^{+5} Dam⁻ organisms. Five weeks post-immunization, the immunized mice were challenged with lethal doses of the virulent strain. Table 5 shows that the immunity elicited by the Dam⁻ vaccine was at least 100-fold greater (3 of 10 mice survived a 10^{+9} challenge) than the immunity elicited in mice that survived an immunization with the wild-type strain (1 of 10 survived a 10^{+7} challenge).

TABLE 4

[00272] Mice immunized with Dam⁻ vaccines elicit greater protection than mice that survive a wild-type infection.

Oral immunization $10+^5$ *S. typhimurium*	Oral challenge with 10^7 wild-type *S. typhimurium*	Oral challenge with 10^8 wild-type *S. typhimurium*	Oral challenge with 10^9 *S. typhimurium*
None	10/10 dead	10/10 dead	10/10 dead
Dam⁺ (at LD_{50})	1/10 alive	10/10 dead	10/10 dead
DamΔ232	5/10 alive	4/10 alive	3/10 alive

[00273] Additionally, immunization with Dam⁻ organisms showed relatively similar levels of protection over a wide range of challenge doses (10^{+7} to 10^{+9}). This suggests that an immunizing dose of 10^{+5} Dam⁻ bacteria is below the minimum threshold of

organisms required to ensure a productive immune response in all immunized animals. It is possible that the enhanced immunity elicited by Dam⁻ strains may be attributed, in part, to the ectopic expression of Dam repressed-antigens, which may not be produced in sufficient quantities and/or duration during a wild-type infection.

[00274] *Immunized animals hinder growth of virulent bacteria in systemic tissues.* Dam⁻ Salmonella were found to be fully proficient in colonization of Peyer's patches of the mouse small intestine but were severely deficient in colonization of deeper tissue sites (liver and spleen) (Example 1). Dam⁻ mutants of *S. typhimurium* are also less cytotoxic to M cells, are deficient in epithelial invasion, and display defects in protein secretion. Pucciarelli et al. (1999) *Proc. Natl. Acad. Sci. USA* 96:11578-11583. Taken together, these data provide a possible explanation as to why Dam⁻ mutants are unable to cause disease but are able to elicit a full-protective immune response. Since mice immunized with Dam⁻ Salmonella showed virtually no overt symptoms of disease after challenge with virulent organisms, the fate of wild-type Salmonella was compared within immunized vs. non-immunized mice. Following a challenge dose of 10,000-fold above the LD_{50}, nonvaccinated mice showed a rapid increase in bacterial number in the Peyer's patches, mesenteric lymph nodes, liver, and spleen, succumbing to the infection on Day 5 (Fig. 7). The data in Fig. 7 show that Dam⁻ immunized mice carry high loads (10^4) of virulent bacteria for at least five days in both mucosal and systemic tissues after wild-type challenge of 10^9 organisms. However, the immunized mice have the ability not only to inhibit the growth of these virulent organisms, they are capable of clearing them from both mucosal and systemic tissues (2 out of 4 mice have cleared all virulent organisms from the Peyer's patches, mesenteric lymph nodes, liver and spleen 28 days post challenge). This ability to clear 10^4 virulent organisms from the liver and spleen is significant in light of the fact that the i.p. LD_{50} is less than 10 organisms. Thus, immunization with Dam⁻ Salmonella hinders the proliferation of wild-type organisms in all tissues tested. The ability to clear a lethal load of virulent bacterium from systemic suggests the possibility that Dam⁻ vaccines may have therapeutic application to the treatment of a pre-existing microbial infections.

[00297] Merodiploid analysis has revealed that, in contrast to *E. coli* and *Salmonella spp.*, Dam was essential for viability in *V. cholerae* and *Y. pseudotuberculosis*. A duplication of *Dam* was constructed by integrating a recombinant plasmid containing a Dam mutation into the wild type Dam locus. The resulting duplication contained two copies of *Dam*: a mutant copy and a wild type copy. Normally, the recombinant plasmid segregates at a given frequency, and there is a roughly equal chance that the recombinants (segregants) contain either the mutant or the wildtype gene. If a gene is essential, all segregants of the duplication (which recombines out of the plasmid) is wild type; the recombinants having the mutant gene die. If a recombinant plasmid containing the gene is present, the duplication can segregate either to the mutant or wild type. For *Vibrio cholerae* and *Yersinia pseudotuberculosis*, duplication of the *Dam* gene to contain both a wild type and a mutant cannot segregate to the mutant unless a recombinant plasmid providing a wild type *Dam* gene is present.

[00298] Dam$^-$ segregants of *Y. pseudotuberculosis* and *V. cholerae* were only obtained in the presence of a wild-type copy of Dam provided in trans, indicating that Dam is essential for viability in both organisms. The *Y. pseudotuberculosis* and *V. cholerae Dam* genes were identified by complementation of 2-amino purine sensitivity of *S. typhimurium Dam* mutants. These complementing plasmid clones were introduced into *Dam*$^-$ *E. coli*. Recovered plasmids were found to be resistant to the methylation-sensitive restriction enzyme, *Mbo*I, indicating that the complementing clones encode the Dam methylase. The *Y. pseudotuberculosis* and *V. cholerae Dam* genes identified encode putative proteins that are 70% and 63% identical over the entire *E. coli* Dam protein, respectively, using the Fasta sequence comparison program of Genetics Computer Group (GCG). Note that the *V. cholerae Dam* gene described in these studies differs from a previously published putative *Dam* sequence, which has 60% identity at the nucleotide level over 250 bp of the 837 bp *E. coli Dam* gene (Bandyopadhyay, R., *et al.*, *Gene*, 140:67-71 (1994)). The *Dam* nucleotide sequences in this study have been deposited in GenBank: accession numbers for *Y. pseudotuberculosis* (AF274318) and *V. cholerae* (AF274317).

TABLE 3

[00265] Oral immunization with Salmonella Dam-based vaccines elicits cross-protective immune responses against heterologous serotypes.

A. Immunization with Dam⁻ S. enteritidis confers cross-protective immunity.

Oral immunization	Oral challenge with 10^9 wild-type *S. dublin*	Oral challenge with 10^9 wild-type *S. typhimurium*	Oral challenge with 10^9 wild-type *S. enteritidis*
No bacteria	20/20 dead	19/19 dead	19/19 dead
S. enteritidis Dam102::Mud-Cm	9/26 alive	7/25 alive	5/26 alive

B. Immunization with Dam⁻ S. typhimurium confers cross-protective immunity.

Oral immunization	Oral challenge with 10^8 wild-type *S. enteritidis*	Oral challenge with 10^9 wild-type *S. dublin*	Oral challenge with 10^8 wild-type *S. dublin*	Oral challenge with 10^9 Wild-type *S. typhimurium*
No bacteria	17/17 dead	25/25 dead	11/11 dead	10/10 dead
S. typhimurium DamΔ232	4/18 alive	4/19 alive	10/19 alive	11/11 alive